Trials

STUDY PROTOCOL

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A multi-center, double-blind, placebo-controlled, randomized, parallel-group, non-inferiority study to compare the efficacy of goal-directed tranexamic acid administration based on viscoelastic test versus preemptive tranexamic acid administration on postoperative bleeding in cardiovascular surgery (GDT trial)

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Abstract

Background Tranexamic acid (TXA) effectively attenuates hyperfibrinolysis and preemptive administration has been employed to reduce bleeding and blood transfusions in various surgical settings. However, TXA administration could be associated with adverse effects, such as seizures and thromboembolic risks. While patients with fibrinolysis shutdown showed greater thromboembolic complications and mortality, TXA administration may aggravate the degree of shutdown in these patients.

Selective TXA administration based on the results of rotational thromboelastometry (ROTEM) would be non-inferior to preemptive TXA administration in reducing postoperative bleeding and beneficial in reducing its risks in patients undergoing cardiovascular surgery.

Methods This non-inferiority, randomized, double-blind, placebo-controlled, multicenter trial will be performed in 3 tertiary university hospitals from August 2023 to March 2025. Seven hundred sixty-four patients undergoing cardiovascular surgery will be randomly allocated to get TXA as a preemptive (Group-P) or goal-directed strategy (Group-GDT) in each institution (with a 1:1 allocation ratio). After anesthesia induction, TXA (10 mg/kg and 2 mg/kg/h) and a placebo are administered after anesthesia induction in Group-P and Group-GDT, respectively. ROTEM tests are performed immediately before weaning from CPB and at the considerable bleeding post-CPB period. After getting the test results, a placebo is administered in Group-P (regardless of the test results). In Group-GDT, placebo or TXA

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is administered according to the results: placebo is administered if the amplitude at 10 min (A10-EXTEM) is ≥ 40 mm and lysis within 60 min (LI60-EXTEM) of EXTEM assay is ≥ 85%, or TXA (20 mg/kg) is administered if A10-EXTEM is < 40 mm or LI60-EXTEM is < 85%. The primary outcome is inter-group comparisons of postoperative bleeding (for 24 h). The secondary measures include comparisons of perioperative blood transfusion, coagulation profiles, reoperation, thromboembolic complications, seizures, in-hospital mortality, fibrinolysis phenotypes, and hospital costs.

Discussion The absence of inter-group differences in postoperative bleeding would support the selective strategy's non-inferiority in reducing postoperative bleeding in these patients. The possible reduction in thromboembolic risks, seizures, and fibrinolysis shutdown in Group-GDT would support its superiority in reducing TXA-induced adverse events and the cost of their management.

Trial registration This trial was registered at ClinicalTrials.gov with the registration number NCT05806346 on March 28, 2023.

Trial status: recruiting.

Issue date: 2023 March 28 (by Tae-Yop Kim, MD, PhD).

The trial was registered in the clinical registration on March 28, 2023 (ClinicalTrials.gov, NCT05806346) and revised to the latest version of its protocol (version no. 8, August 26, 2024) approved by the institutional review boards (IRBs) of all 3 university hospitals (Konkuk University Medical Center, 2023–07-005–001, Asan Medical Center, 2023–0248, and Samsung Medical Center, SMC 2023–06-048–002). Its recruitment was started on August 1, 2023, and will be completed on December 31, 2024.

Protocol amendment number: 08 (protocol version 08, August 26, 2024).

Revision chronology:

2023 March 28:Original.

2023 April 10:Amendment No 01. The primary reason for the amendment is the modification of Arms (adding one arm for sub-group analyses) and Interventions, Outcome Measures, Study Design, Study Description, Study Status, Eligibility, and Study Identification.

2023 May 03:Amendment No 02. The primary reason for the amendment is to modify the Outcome Measures and update the study status.

2023 July 06:Amendment No 03. The primary reason for amendment is to update the chronological study status.

2023 July 07:Amendment No 04. The primary reason for the amendment is the modification of study information (the treatment category was changed to diagnostic, and Phase 4 was changed to not applicable) and a chronological update on the study status.

2023 September 12:Amendment No 06. The primary reason for the amendment is a chronological update in the study status and the inclusion of additional information regarding contacts/locations and oversight.

2023 December 29:Amendment No 07. The primary reason for the amendment is to modify the outcome measures (including detailed information on outcome measures, addition of extra secondary measures, and chronological updates in study status).

2024 August 26:Amendment No 08. The primary reason for the amendment is to add detailed descriptions regarding data handling and the names and roles of the participating institutions and to update the chronological process of the trial.

Keywords Cardiac surgery, Clinical trial, Goal-directed, Rotational thromboelastometry, Tranexamic acid, Viscoelastic test

Background

Tranexamic acid (TXA) is an antifibrinolytic agent that has been regarded to reduce the amount of surgical bleeding, allogenic blood transfusions, and deaths from bleeding in perioperative settings. Most major guidelines recommend the routine use of TXA during surgeries with a higher risk of bleeding, such as cardiovascular surgery [1, 2]. The preemptive TXA administration has been widely adopted in managing surgeries with a high risk of bleeding.

However, despite the recent meta-analysis reporting the absence of increased thromboembolic events and mortality [3], it is still debated whether preemptive TXA administration is free from the risks of increasing mortality and inducing thromboembolic events in various clinical settings [4–7].

Another concern is that TXA can dose-dependently increase the risk of seizures in cardiac surgery [8–10]. TXA-induced seizures would be assumed as clinically negligible and the benefit of TXA administration can exceed its risks [11]. However, even a clinically non-significant form of postoperative seizure warrants meticulous evaluation and management, such as neurological consultation with EEG monitoring, brain imaging, anticonvulsant prescription, all leading to increased cost and hospital stay.

TXA administration is to improve fibrin clot strength and reduce bleeding by attenuating hyperfibrinolysis in various clinical settings. However, a certain phenotype of three different fibrinolysis phenotypes, such as physiologic fibrinolysis, hyperfibrinolysis, and fibrinolysis shutdown, increases mortality [12, 13]. Furthermore, in trauma settings, TXA administration in a certain phenotype increases multi-organ failure (MOF) [14] and mortality [15] and showed beneficial effects only in patients with hyperfibrinolysis [16, 17].

In the meantime, ischemia–reperfusion induces hyperfibrinolysis by plasminogen activator (tPA) in the ischemic endothelium in surgical settings. However, tissue injury by surgical procedures can induce fibrinolysis shutdown [18]. In these contexts, a strategy with selective TXA administration according to the underlying fibrinolysis phenotypes would be desirable in cardiac surgery patients. At least, TXA administration may have to be avoided in these patients with fibrinolysis shutdown [12, 16].

As in managing acutely injured patients [18], point-of-care (POC) viscoelastic tests (VET), such as rotational thromboelastometry (ROTEM) and thromboelastography (TEG), would enable earlier determination of fibrinolysis phenotype [19] and prompt effective antifibrinolytic therapy.

Therefore, the present trial hypothesizes that the ROTEM-guided goal-directed TXA administration would be non-inferior to the preemptive TXA administration in reducing postoperative bleeding in cardiovascular surgery. The author also hypothesized that goal-directed TXA administration would be superior in reducing or avoiding undesirable effects of risk of TXA administration, such as postoperative thromboembolic events, seizures, fibrinolysis shutdown, and mortality.

Methods/design

The aim, design, and setting of the trial

This trial is an investigator-initiated, randomized, double-blind, placebo-controlled, parallel 2 groups with a 1:1 allocation ratio, multicenter, pragmatic, non-inferiority trial and conducted in 3 tertiary university hospitals in Seoul, South Korea, for 18 months, from August 1, 2023, to March 31, 2025. As a non-inferiority trial, it hypothesized that the postoperative blood loss in employing a ROTEM-guided goal-directed TXA administration based on the ROTEM test would be non-inferior to that in preemptive TXA administration in patients undergoing elective cardiovascular surgery. It also compares intergroup differences in allogeneic blood transfusion, lowest hemoglobin value, reoperation due to postoperative bleeding, perioperative coagulation profiles, incidences of thromboembolic complications, postoperative seizures, and hospital costs. The perioperative data are conveyed to the contract research organization (CRO, Helptrial Co., Seoul, Korea) using an electronic case report form (e-CRF, product name™, Helptrial Co., Seoul, Korea). An overview of the processes for trial enrollment, treatment, and follow-up is shown in Fig. 1. The conveyed data are kept and opened for analysis after the discharge of the last participating patients.

Protocol modification could be considered at all investigators' requests only during the first week of recruitment at each institution. Since the trial is a pragmatic design for evaluating the effectiveness of ROTEM-guided TXA administration in clinical settings, apart from the TXA administration, strategies and disciplines for perioperative patient management, such as surgical procedures, anesthesia, transfusions, and coagulation management, are not strictly controlled. However, institutional protocols for perioperative transfusion and coagulation management are based on current guidelines [20, 21].

Trial status

The trial was registered in the clinical registration on March 28, 2023 (ClinicalTrials.gov, NCT05806346) and revised to the latest version of its protocol (version no. 8, August 26, 2024) approved by the institutional review boards (IRBs) of all 3 university hospitals (Konkuk University Medical Center, 2023–07-005–001, Asan Medical Center, 2023–0248, and Samsung Medical Center, SMC 2023–06-048–002). Its recruitment was started on August 1, 2023, and will be completed on December 31, 2024.

Eligibility for participants and informed consent

Adult patients scheduled for an elective cardiovascular surgery will be eligible for enrolment. Detailed eligibility and exclusion criteria are as follows: inclusion

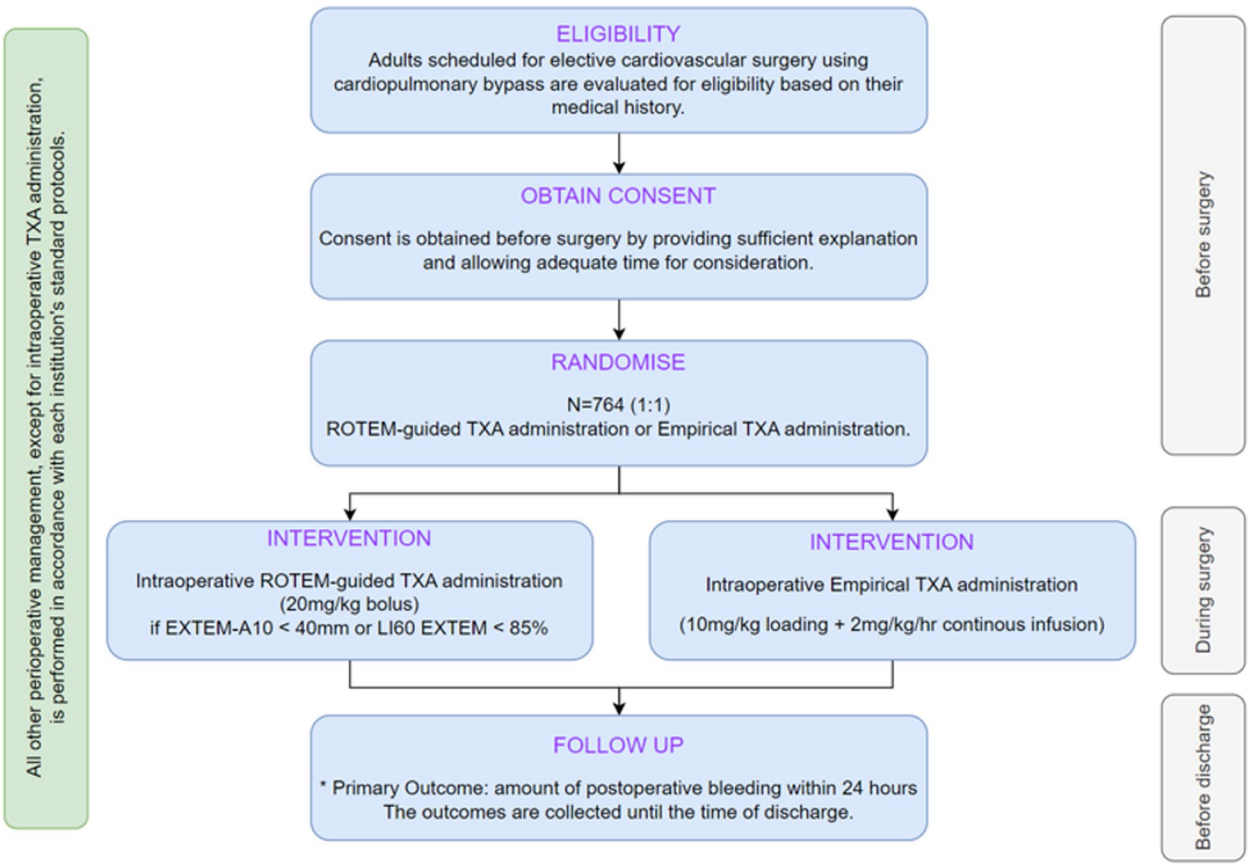

Fig. 1 Study flow chart for eligibility, randomization, intervention, and follow-up. TXA, tranexamic acid

criteria include adult patients undergoing elective cardiovascular surgery and patients who signed informed consent for the study. Written, informed consent to participate will be obtained from all participants during the preoperative visit.

Exclusion criteria include pregnancy, refusal of allogenic blood transfusion, thrombin medication, history of myocardial ischemia infarction or ischemic stroke within 90 days, history of thromboembolism, familial history of hypercoagulation, history of allergic responses to TXA, dialysis due to the end-stage renal disease, history of convulsions and epilepsy, and heparin-induced thrombocytopenia.

The primary investigator, single senior investigators in each institution, and certified research associates are responsible for screening patients eligible for inclusion. All investigators (anesthesiologists) explain trial details and obtain written informed consent from potential eligible participants.

Randomization and blinding of participants

The randomization sequence was generated using a computerized random number generator by an independent statistician in the CRO. The participants are assigned to either Group-GDT or Group-P (1:1) through the web-based randomization system managed by the CRO (https://icreat2.nih.go.kr/). Randomization is stratified by institution and types of surgery with variable block sizes.

In each institution, a senior investigator, who monitors each institutional protocol, refrains from making any perioperative management and oversees the randomization process. The senior investigator prepares the combinations for group assignments and delivers study drugs to the anesthesiologists who care for the enrolled participant in the operating room. Other investigators cannot access the randomization sequences and the group assignment, which are secured on the web-based randomization system, till the end of data acquisition. The group assignment also remains confidential and blinded to the following individuals: participants, attending anesthesiologists and nursing staff, surgeons, medical staff in the intensive care unit, and outcome assessors. However,

if unblinding is beneficial in patients' clinical outcomes or is necessary for patient management in a certain case, the information on the group assignment can be disclosed. All unblinded cases are reported to the principal investigator and excluded from the per-protocol analysis.

Patient withdrawal

Every reasonable effort will be made to maintain protocol compliance and retain patient participation in the trial. Participation can be terminated if the patient wants to withdraw from the study. The reason for withdrawal is reported. All withdrawn participants will be managed in accordance with the institutional standard procedures.

TXA or placebo administration

For blinding TXA or placebo administration, the senior investigator responsible for the group assignment prepares the first and second study solutions, which are only labeled as "Solution-1" and "Solution-2" and do not specify which drug is contained in either solution. Solution-1 and Solution-2 are 0.9% NaCl 100 ml containing TXA 2.0 g (TXA solution) or 0.9% NaCl 100 ml alone (placebo).

Solution-1 is TXA solution in Group-P and Placebo in Group-GDT, respectively. Before anesthesia induction, Solution-1 is delivered to attending anesthesiologists in the OR who are blinded to the patient group allocation and administered in a bolus (0.5 ml/kg) after anesthesia induction and continuously infused (0.1 ml/kg/h) till the end of its infusion.

The ROTEM test is performed at least 3 times, after anesthesia induction, immediately before weaning from CPB, and at the end of surgery. Additional ROTEM tests can be performed at the need of the attending anesthesiologist. The investigator responsible for the group assignment prepares Solution-2, which is the placebo or TXA solution according to the group and the results of the ROTEM test: it is always placebo in Group-P, regardless of the results of the ROTEM test; by contrast, it is either the placebo or TXA solution according to the results of the intraoperative ROTEM test in Group-GDT. Solutioin-2 is placebo in Group-GDP patients with the EXTEM amplitude at 10 min (A10-EXTEM) $\geq$ 40 mm and lysis within 60 min in EXTEM assay (LI60-EXTEM) $\geq$ 85% (these patients are defined as "Subgroup-GDT0"), and TXA solution in those patients with A10-EXTEM is < 40 mm or LI60-EXTEM in EXTEM assay is < 85% (these patients are defined as "Subgroup-GDT1"). Solution-2, delivered to the blinded anesthesiologists, is administered in a bolus of 1.0 ml/kg for 10 min, and the remaining volume of Solution-2 is returned after the administration.

If there is diffuse oozing or massive bleeding, open-label TXA administration is allowed, at the discretion of the attending anesthesiologists, and the additional dosage of TXA is recorded.

Figure 2 summarizes the study interventions.

The principal investigator, senior investigators, CRO, and the data and safety monitoring boards (DSMB) monitor the adherence to the trial protocol and exclude non-adherence cases from the pre-protocol analysis. The primary investigator will access the final data registry after all data acquisition and storage.

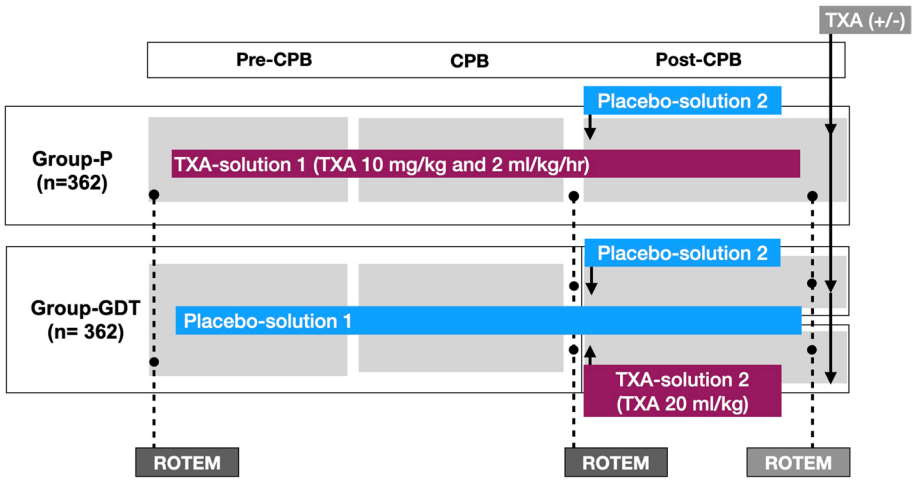

Fig. 2 Interventions during surgery. TXA, tranexamic acid; Placebo, 0.9% Group-P, patients taking preemptive TXA administration; Group-GDT, patients taking ROTEM-guided TXA administration; ROTEM, rotational thromboelastometry; CPB, cardiopulmonary bypass; Pre-CPB; pre-CPB period; post-CPB, post-CPB period

Rationale for TXA dosages

A low dose of TXA (total 20 mg/kg) was sufficient to reduce postoperative blood loss and erythrocyte transfusion, and it was associated with relatively decreased seizure incidence compared to higher dosages in cardiovascular surgery [22]. The latest European guidelines also recommend a TXA dosage of no more than 20 mg/kg in cardiac surgery [23]. Accordingly, the trial employs 20 mg/kg of TXA in Group-GDT. Considering the longer TXA infusion period (extended to the pre-CPB and CPB period), it employs a modified low-dose regimen comprising TXA 10 mg/kg and infusion (2mg/kg/hr) in Group-P [9].

Anesthesia and surgery

The trial adopts a pragmatic design to evaluate the effectiveness of ROTEM-guided TXA administration in real clinical settings. Pragmatic studies are typically conducted without strict clinical trial conditions to evaluate interventions in a variety of settings. Therefore, apart from the administration strategy for TXA, all other treatment strategies, including surgical procedures, anesthesia, transfusions, and coagulation management, follow institutional protocols established in consideration of current practice guidelines [20, 21].

Preoperative management, anesthetic, and surgical techniques follow institutional protocols. The surgical procedures are performed under general anesthesia. A mild to moderate hypothermic CPB is applied. Heparin (300 IU/kg) will be intravenously administered before initiation of CPB, with activated clotting time (ACT) maintained above 400 s during CPB. After CPB, circulating heparin will be antagonized with protamine sulfate at a ratio of 0.75–1 mg of protamine per 100 IU of heparin.

The trial employs the institutional standards for undergoing cardiovascular surgery, and perioperative ROTEM-based bleeding management algorithm [21].

Intraoperative cell salvage will be applied during surgery.

Study outcomes

The trial compares clinically meaningful and objective outcome measures.

The primary outcome of the study is the comparison of the amount of postoperative bleeding collected in the chest drainage during postoperative 24 h. Secondary outcomes include the incidences and total amounts of intraoperative and postoperative allogeneic transfusions (packed red blood cells, fresh frozen plasma, platelets, and cryoprecipitate), amount of intraoperative salvaged blood, postoperative nadir hemoglobin value, reoperation due to bleeding, and perioperative coagulation profiles (standard laboratory tests and ROTEM, as well as the distribution of fibrinolysis phenotypes). Tertiary prognostic outcomes include postoperative death,

Table 1 Primary and secondary outcomes

Outcomes	Definition
Primary outcome	
Postoperative bleeding	Volume of postoperative bleeding collected in the chest drainage during the first 24 h after surgery (mL)
Secondary outcomes	
Incidence of transfusion	Patients who had intraoperative and postoperative transfusion until discharge: packed RBC, FFP, platelet, and cryoprecipitate (number of patients, %)
Amount of transfusion	Amount of intraoperative and postoperative transfused packed RBC, FFP, platelet, and cryoprecipitate per patients until discharge (units)
Amount of intraoperative salvaged blood	Volume of intraoperatively salvaged and reinfused blood (ml)
Postoperative nadir hemoglobin value	Lowest hemoglobin level measured during the first 24 h after surgery (g/dl)
Reoperation due to bleeding	Patients who underwent reoperation due to postoperative bleeding (number of patients, %)
Perioperative coagulation profiles	The following coagulation profiles will be compared immediately after anesthesia induction, before weaning from cardiopulmonary bypass, and at the end of surgery
Standard laboratory test	Hemoglobin (g/dL), D-dimer (mg/l), prothrombin time (INR), activated partial thromboplastin time (sec), serum fibrinogen level (mg/dl), and platelet counts (/μL)
ROTEM test	Values of ROTEM tests including CT-EXTEM (sec), CTF-EXTEM (sec), A5-EXTEM (mm), A10-EXTEM (mm), A15-EXTEM (mm), MCF-EXTEM, LI60-EXTEM (%), CT-FIBTEM (sec), CTF-FIBTEM (sec), A5-FIBTEM (mm), A10-FIBTEM (mm), A15-FIBTEM (mm), MCF-FIBTEM (mm), LI60-FIBTEM (%), A5-PLTEM (mm), and A10-PLTEM (mm)
Fibrinolysis phenotypes	Hyperfibrinolysis: LI60-EXTEM of < 85% Physiologic fibrinolysis: LI60-EXTEM of 85–97.9% Fibrinolysis shutdown: LI60-EXTEM of ≥ 98%

CT clotting time, *CTF* clot formation time, *EXTEM* extrinsically-activated test with tissue factor, *FIBTEM* fibrinogen-specific test, *A5* amplitude at 5 min, *A10* amplitude at 10 min, *A15* amplitude at 15 min, *LI60* lysis at 60 min, *PLTEM*, estimated value calculated by EXTEM–FIBTEM

Table 2 Tertiary prognostic outcomes

Outcomes	Definition
Postoperative death	Death due to any cause during hospitalization (number of patients, %)
Myocardial infarction	Patients with following episodes: type 5 periprocedural myocardial infarction within postoperative 48 h defined by Valve Academic Research Consortium (VARC) 3; in patients with normal baseline CK-MB, the peak CK-MB measured within 48 h of the procedure ≥ 10 × the local laboratory ULN or CK-MB ≥ 5 × ULN with one or more of the following: new pathologic Q-waves in ≥ 2 contiguous lead, new persistent LBBB, flow-limiting angiographic complications in a major epicardial vessel or > 1.5 mm diameter branch, substantial new loss of viable myocardium on imaging related to the procedure. In the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the procedure rises to ≥ 70 × the local laboratory ULN or ≥ 35 × ULN with one or more of the above criteria. In patients with elevated baseline CK-MB (or cTn), the CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus new ECG changes as described (number of patients, %)
Stroke	Patients with following episodes until discharge: sudden onset of neurological signs or symptoms with neuroimaging confirmation of CNS infarction in the corresponding vascular territory; symptomatic ICH and SAH; symptomatic hypoxic-ischemic injury (non-focal neurological signs or symptoms due to diffuse brain, spinal cord, or retinal cell death confirmed by neuroimaging); or persistent (> 24 h) neurologic deficit presumed to be ischemia or hemorrhage (e.g., no neuroimaging) (number of patients, %)
Pulmonary embolism	Definite pulmonary embolism in the enhanced CT or angiogram or high probability ventilation-perfusion scan until discharge (number of patients, %)
Bowel infarction	Bowel resection surgery or bowel infarction confirmed by imaging until discharge (number of patients, %)
Seizure	Acute onset of generalized tonic–clonic activity or myoclonic movements until discharge (number of patients, %)
Delirium	Positive screening result on the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) or a diagnosis confirmed by psychiatrist or neurologist until discharge (number of patients, %)
Acute kidney injury	Defined by KIDGO serum creatinine criteria; 0.3 mg/dL increase within 48 h or ≥ 1.5 times baseline within 7 days (number of patients, %)
Renal replacement therapy	Need for renal replacement therapy until discharge (number of patients, %)
Mechanical circulatory support	Need for mechanical circulatory support such as extracorporeal membrane oxygenation, intra-aortic balloon pump, ventricular assist device until discharge (number of patients, %)
Duration of mechanical ventilation	Total time (hour) a patient supported by a mechanical ventilator
Length of the ICU stay	Total time (hour) a patient spends in the ICU from admission to discharge
Length of the hospital stay	Total time (day) a patient spends from surgery to discharge
Total cost	Total cost associated with a patient's entire hospital stay
Seizure-related cost	Cost related to seizure (e.g., electroencephalogram, neuroimaging, antiepileptic drug, consultation fees)

CAM confusion assessment method, *cTn* cardiac troponin, *ICU* intensive care unit, *KIDGO* Kidney Disease Improving Global Outcomes, *UNL* upper limit of normal, *LBBB* left bundle branch block

myocardial infarction, stroke, pulmonary embolism, bowel infarction, seizure, delirium, acute kidney injury, renal replacement therapy, applications of mechanical circulatory support, duration of mechanical ventilation, length of intensive care unit and hospital stay, total cost, and additional expenses due to seizure-related costs (e.g., EEG monitoring, neuroimaging, antiepileptic drugs, consultation fee). Detailed definitions of the outcomes are provided in Table 1 and Table 2.

Data acquisition and follow-up

Data collected in each institution are conveyed to the CRO data registry through e-CRF. The participant's follow-up is scheduled 24 and 48 h after surgery, discharge, or death. The trial is performed independently in three institutions according to a pre-determined ratio of patient recruitment. The trial steering committee (TSC), which consists of the primary and senior investigators of each institution, reviews the course of the trial to oversee its conduct and progress and provides feedback to all institutions every month. There is no stakeholder and public involvement group (SPIG). Adverse events and serious adverse events (SAE) are monitored and collected. The CRO independently monitors the conveyed data from all participating institutions and keeps the data confidential in the registry. The CRO is independent from the sponsor and competing interests.

Patient data are entered into a blank e-CRF in a web-based data entry program. The data in each institution are collected and delivered to the CRO through the web-based system (MyTrial™, San Diago, USA). The data are stored after repeated query management processes between the CRO and senior investigators. The participant's postoperative follow-up is scheduled regularly.

The CRO independently manages the conveyed data from all participating institutions and keeps the data confidential by locking the database until the end of patient recruitment. After locking, it can be unlocked only when

a query is issued or an erroneous data entry is indicated. After resolving the query and completing data modification or correction, the database is relocked.

The CRO performs medical coding when data entry is completed and when the rate of erroneous data is acceptable (at least less than 0.1%).

Sample size calculation

The trial was designed as a non-inferiority trial, hypothesizing that the mean postoperative 24-h bleeding in Group-GDT would be non-inferior to that of Group-P. In previous studies using TXA on the bleeding in cardiac surgery [8, 10], the minimum effect of TXA administration on reducing the postoperative 24-h bleeding (the chest tube drainage during postoperative 24 h) was around 200 ml. Investigators set the non-inferiority margin of the present trial as 100 ml, which is 50% of the minimum effect in the previous study [8]. Additionally, we estimated that the standard deviation of the postoperative bleeding would be approximately 480 ml.

The sample size was 724 patients (362 patients per group) to achieve a 2.5% one-sided significance level (α) and 80% power (1-β) with the following assumptions: an expected inter-group difference of the mean postoperative bleeding is 0 ml, and a non-inferiority margin is 100 ml with the standard deviation of 480 ml in both groups. Considering a dropout rate of 5% after recruitment, 764 patients (382 patients per group) are recruited in total. The sample size was calculated using PASS 15 program™ (NCSS, Kaysville, UT, USA).

Statistical analyses

All primary analyses will be performed on an intention-to-treat basis (defined as all subjects randomized, regardless of the treatment actually received). Secondary analyses will be performed in the as-treated population (defined as patients who actually received treatment, regardless of the randomized assignment) and the per-protocol population (defined as randomized patients excluding subjects for non-compliance, non-adherence, or missing data).

Continuous variables will be summarized with descriptive statistics such as mean and standard deviation, and differences between groups will be confirmed using *t*-test or Wilcoxon rank sum test. Categorical variables will be reported as numbers and percentages and differences between groups will be compared using the χ^2 statistics or Fisher exact test, as appropriate.

For the primary outcome, non-inferiority will be assessed using a one-sided 97.5% confidence interval (CI) for the mean difference and a non-inferiority margin (=100 ml). We will also calculate the difference between the median and 95% CI for the primary outcome using the independent samples Hodges-Lehmann estimator.

Except for the primary outcome, all reported *p* values will be 2-sided, and a p-value < 0.05 will be considered statistically significant. Statistical analyses will be performed with SAS version 9.4 (SAS Institute) and R version 4.3.2 or higher (R Foundation for Statistical Computing).

Handling of missing data

For the intention to treat analysis, missing data or dropout occurs at a certain time point during the study period before the study is completed and will be replaced. The method of replacing missing data will be used in two extreme scenarios. In the worst-best-case scenario analysis, all dropout patients in the experiment group showed the maximum bleeding amount of the experiment group, and all dropout patients in the control group were replaced as non-bleeding. In the best–worst-case scenario analysis, the opposite assumptions are applied. If there is a discrepancy between the two extreme analyses, multiple imputation methods are implemented to find the "tipping point" [24]. In addition, if the data collection of postoperative bleeding was stopped due to reoperation, the analysis is performed on the assumption that the amount of bleeding immediately before the reoperation continued, and sensitivity analysis is additionally performed on the assumption that the last bleeding continues twice or three times.

Adverse events and their monitoring

Any unexpected adverse event not included in the trial outcomes will be reported through the e-CRF form by the participants or attending anesthesiologists, surgeons, and nursing staff. The CRO regularly conveys the event to the primary investigator and the Korea Health Industry Development Institute, which includes experts for anesthesia practice and anesthetic pharmacology, free of conflict of interest, every month to get feedback from the data and safety monitoring boards (DSMB). All adverse events will be reported to the CRO and the DSMB. DSMB audits the reported data related to adverse events.

Serious adverse event (SAE) is defined as any untoward medical occurrence or effect that results in death, is life-threatening (at the time of the event), prolongs the length of hospital stay, or results in persistent or significant disability or incapacity or any other important medical event that does not result in any of the outcomes listed above. SAEs are directly reported to the PI and the DSMB, and the follow-up data should be reported after 24 h. The trial will be paused till the judges of the DSMB allow it to continue. SAEs are also reported to the IRB within 24 h.

Provision for post-trial care

All participants who suffered any harm will be compensated by the coverage of the contracted insurance company (Hyundai Marine and Fire Insurance Group, contract number F-22CT-0000121).

Funding

The study is funded by a grant from the Korea Health Technology Research and Development through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant number: HI22C1952). This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Sponsor

The Konkuk University Medical Center sponsors this study and performs study design, data collection, and management. As collaborators, the Asan Medical Center performs study design, data collection, and management. The Samsung Medical Center performs study design, data collection, and management. Helptrial Co. performs data collection and management as a CRO.

Composition of the coordinating center and trial steering committee

Data collected in each institution are conveyed to the CRO data registry through e-CRF. The participant's follow-up is scheduled 24 and 48 h after surgery, discharge, or death.

The trial is performed independently in three institutions according to a pre-determined ratio of patient recruitment. The trial steering committee (TSC), which consists of the primary and senior investigators of each institution, reviews the course of the trial to oversee its conduct and progress and provides feedback to all institutions every month. There is no stakeholder and public involvement group (SPIG).

Adverse events and serious adverse events (SAE) are monitored and collected.

The CRO independently manages and monitors the conveyed data from all participating institutions and keeps the data confidential in the registry. The CRO is independent from the sponsor and competing interests.

The trial does not have any committee for these issues. Data collected in each institution are conveyed to the CRO data registry through e-CRF. The CRO regularly monitors and keeps the conveyed data till the end of data acquisition.

Discussion

Routine antifibrinolytic therapy was advocated to manage systemic fibrinolysis identified by TEG during the anhepatic phase of liver transplantation [25]. However, transplant survivors after taking antifibrinolytic therapy (aminocaproic acid) developed multiple pulmonary emboli [26] and required fibrinolytic therapy [27]. During the three decades, fibrinolytic therapy became the standard for managing arterial thromboembolic events in the coronary, cerebral, mesenteric, and peripheral vasculature.

On the other side, the widespread availability of TEG contributed to determining excessive fibrinolytic conditions in perioperative stings. However, the enthusiasm for administering antifibrinolytics was dampened after the increased incidence of renal failure, myocardial infarction, and mortality in the use of an antifibrinolytic agent (aprotinin) for CABG surgery [28]. As in the use of other antifibrinolytics, it would be difficult to overlook the possible association of TXA-induced thromboembolic risks, such as stroke, myocardial infarction, pulmonary embolism, and bowel infarction, and mortality [5, 6].

As aforementioned, preemptive administration of TXA has become a routine regimen for surgery with a higher risk of bleeding since its benefits would outweigh its risks. The greatest benefit of TXA administration is the reduction of perioperative bleeding by attenuating hyperfibrinolysis-induced excessive perioperative bleeding and allogenic transfusion, which has greater risks of increasing patients' morbidities. Therefore, TXA contributes to reducing early and late morbidities, bleeding, and transfusion-related risks, respectively, during surgeries with a higher risk of bleeding, as in cardiac surgery. The absence of an increase in thromboembolic events and mortality upon using a wide range of TXA dosages (10–100 mg/kg) in patients of any medical discipline also supported the preemptive use of TXA [3].

Even a clinically non-significant form of postoperative seizure warrants meticulous neurological evaluation and brain imaging, leading to increased cost and hospital stay. Seizure and TXA dosage was variable, dosage-dependent [29–31], or unrelated to the dosage [8, 32]. The trial employs TXA 10 mg/kg bolus and 2 mg/kg/h for all patients in Group-P and TXA 20 mg/kg for selective patients in Group-GDT, respectively.

Timely TXA administration would benefit patients with hyperfibrinolysis and reduce much earlier mortality due to perioperative bleeding. On the other hand, fibrinolysis shutdown is an independent risk factor increasing early death and death before hospital discharge [15], and persistent shutdown increases late mortality in trauma [13]. Fibrinolysis shutdown associated with hypercoagulability

develops microvascular occlusion which induces organ dysfunction [33]. Furthermore, TXA administration increased multi-organ failure in severely injured patients with fibrinolysis shutdown [14]. TXA would affect the fibrinolysis phenotypes and may affect the incidence of fibrinolysis shutdown. Even in trauma patients showing hyperfibrinolysis, avoidance or judicious use of TXA was advocated [34, 35].

Therefore, TXA may have to be avoided in patients with fibrinolysis shutdown and selectively employed according to the type of fibrinolysis phenotypes. Of interest, most patients with fibrinolysis shutdown showed the absence of hyperfibrinolysis with moderate coagulopathy in trauma patients [15]. These patients require pro-coagulant therapy, rather than antifibrinolytics, such as TXA.

This trial will provide valuable insight regarding the impacts of TXA administration on adverse outcomes, including thromboembolic events and mortality in cardiovascular surgery. It will also provide the impact of TXA administration on the fibrinolysis phenotype in these patients.

Since the fibrinolysis status is very dynamic, its real-time assessment would be difficult by determining D-dimer and plasmin-antiplasmin activity during cardiovascular surgery. While VET, such as ROTEM or TEG, has been employed for prompting goal-directed bleeding management in cardiovascular surgery [21, 36], it may be the best method to identify fibrinolysis phenotype at this moment, as shown in the trauma [16, 17]. In cardiovascular surgery, ROTEM test can provide valuable information regarding the dynamic changes in fibrinolysis status during and after CPB periods. The three fibrinolysis phenotypes, including hyperfibrinolysis, physiology fibrinolysis, and fibrinolysis shutdown, can be determined by the ROTEM as follows: EXTEM-LI60 of < 82%, 82–97.9%, and ≥ 98%, respectively, or the maximum lysis of EXTEM (ML-EXTEM) < 85%, 85–97%, and 97%, respectively [37]. ROTEM-based algorithm effectively determines coagulopathy and hyperfibrinolysis, indicating the uses of procoagulations and TXA for bleeding management [21].

This prospective, double-blind randomized controlled clinical trial is the first trial to compare the efficacy and risk of two TXA administration strategies, ROTEM-guided goal-directed TXA administration and preemptive TXA administration in cardiac surgery.

The trial compares postoperative bleeding, as the primary measure. If there is no significant inter-group difference, the selective strategy is not inferior to the preemptive strategy in perioperative bleeding management in cardiac surgery. The trial also compares the impact of both strategies on patient safety by comparing the incidences of adverse outcomes, such as thromboembolic risks, seizure, and fibrinolysis phenotypes. Inter-group differences in the incidences may be the key elements that support the superiority in reducing TXA-induced risks and adverse events.

Abbreviations

A5	Amplitude at 5 min
A10	Amplitude at 10 min
A15	Amplitude at 15 min
ACT	Activated clotting time
BDSM	Board for data safety and monitoring
CABG	Coronary artery bypass graft
CT	Clotting time
CTF	Clot formation time
cTn	Cardiac troponin
CPB	Cardiopulmonary bypass
CRO	Clinical research organization
e-CRF	Electronic case report form
EEG	Electroencephalography
EXTEM	Extrinsically-activated test with tissue factor
FIBTEM	Fibrinogen-specific test
Group-GDT	Group of goal-directed tranexamic acid administration
Group-P	Group preemptive tranexamic acid administration
KHIDI	Korea Health Industry Development Institute
LI60	Lysis index at 60 min
MCF	Maximum clot firmness
ML	Maximum lysis
MOF	Multi-organ failure
PLTEM	Estimated value calculated by EXTEM–FIBTEM
POC	Point-of-care
VET	Viscoelastic test
ROTEM	Rotational thromboelastometry
SAE	Serious adverse event (SAE)
TEG	Thromboelastography
TXA	Tranexamic acid
UNL	Upper limit of normal
VARC	Valve Academic Research Consortium

Supplementary Information

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Supplementary Material 1.

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Additional consent provisions for collection and use of participant data and biological specimens
The trial does not consider to collect or use participant data and biological specimens in ancillary studies.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic of molecular analysis in this/future use
These issues were not described because the current trial does not store biological specimen for other purposes.

Interim analyses
The trial did not consider performing an interim analysis. The primary investigator will access the final data registry after all data storage.

Authors' contributions
J. N., C. O., T. K., and I. C. contributed to the trial conception and design, data collection, analysis and interpretation of results, and manuscript preparation. S. Y. contributed to the trial conception and design as well as the analysis and interpretation of results. D. C., A. O., J. P., J. L., and M. J. contributed to the trial conception and design and data collection. K. K. contributed to the trial design and manuscript preparation. All authors read and approved the final

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Availability of data and materials
All data and materials will be available in ClinicalTrials.gov after the completion of the trial.

Declarations

Ethics approval and consent to participate
This trial was approved by IRBs in all participating institutions.

Consent for publication
Not applicable—no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent forms are available from the corresponding author on request.

Competing interests
All authors and investigators do not have any conflict of interest related to this trial.

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